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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LIU, SUE XU	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/988,899	HOOGENBOOM, HENDRICUS RENERUS JACOBUS M	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,11,12,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 11, 12, 15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Please note the change of examiner for this application. (Please see the Conclusion paragraph for information on any future correspondence.)

Claim Status

Claims 1-3, 11, 12, 15 and 16 are currently pending;

Claims 1-3, 11, 12, 15 and 16 are being examined in this application.

Applicant's Response

1. Applicant's response filed on 3/31/2006 has been fully considered and entered in the application. No amendment to the claims was made by the applicant.

Claim Rejections Maintained

Claim Rejections - 35 USC § 102

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1-3, 11-12, 15-16 are rejected under 35 U.S.C. **102(e)** as being anticipated by US Patent 5,969,108 (McCafferty et al) (filing date Jan 1993) ((hereinafter referred to as the **'108 patent)**. The previous rejection is maintained for the reasons of record advanced on page 4 of the office action mailed on 12/29/2005.

Discussion and Answer to Argument ('108 patent)

4. *Applicant argues that the examiner failed to consider all of the limitations of the instant claims and thus mis-characterized the instant claims. The instant claims are directed to a library made up of a collection of vectors. The individual vectors have common features (e.g., first and second cloning regions, a sequence encoding an anchor region, and a tag) and unique features (e.g., the first and second pluralities of variable polynucleotides). The first and second pluralities of variable polyucleotides each encode a plurality of polypeptides (i.e., the first plurality of variable polynucleotides encodes a first plurality of polypeptides and the second plurality of variable polynucleotides encodes a second plurality of polypeptides). Both the first and second pluralities are variable, and thus neither the nucleotide sequences nor the polypeptide sequences encoded by them are "fixed" (Pg 2-3 of the reply filed 3/31/06).*

5. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record):

Claim interpretation

The claim language of the instant application is unclear and convoluted, and renders multiple interpretations. Generally, the instant claims are drawn to a plurality (or a library) of vectors with each vector comprising:

i. "a member of a first plurality of variable polynucleotides", i.e. a single variable polynucleotide. The first plurality of variable polynucleotides encode a first plurality of polypeptides. Therefore, each member of the first plurality of variable polynucleotides encodes for a variable domain (such as either light or heavy chain variable region) of an antibody.

ii. "a member of a second plurality of variable polynucleotide", i.e. a single variable polynucleotide; The second plurality of variable polynucleotides encode a second plurality of polypeptides. Therefore, each member of the second plurality of variable

polynucleotide encodes for a variable domain (such as either light or heavy chain variable region) of an antibody.

iii. Other elements including an anchor region, ribosome binding sites (one in each cloning region), signal sequences (one in each cloning region), restriction sites (one in each cloning region), and a tag region.

The claim (Claim 1) recites "a member of a first (or second) plurality of variable polynucleotides", which limits each one of the vector within the library to comprise only a single first member and a single second member derived from the pluralities of first and second members. The claim does not recite that the vectors comprise a first plurality of variable polynucleotides and further comprise a second plurality of variable polynucleotides, as applicant seems to argue.

In addition, the instant claim (Claim 1) also recites "the polypeptides of each of said first and second pluralities being selected from the group consisting of a complete antibody variable region ..." (emphasis added). This limitation can be interpreted to mean that each of the first and second pluralities of polypeptides is a single complete antibody variable region, i.e. a variable region derived from a single antibody. Therefore, each of "plurality" of polypeptides (or the encoding polynucleotides) can be interpreted as a collection of multiple polypeptides (or the encoding polynucleotides) that have the same antibody variable region.

Reference's teaching ('108 patent)

Applicant mainly argues that the '108 patent does not teach every elements recited in the instant claims. Contrary to applicant's assertion, the cited reference ('108 patent) teaches

individual vectors (i.e. each single vector) comprising "a member of a first plurality of variable polynucleotides" and "a member of a second plurality of variable polynucleotides". The '108 patent teaches a library of vectors comprising a combination of heavy and light chain variable regions (corresponding to a member of a first (or second) plurality of variable polypeptides) (see the Examples 1-48 of the reference). For example, in Example 22, the reference teaches the generation of a library of vectors with each vector comprising a heavy and a light chain variable regions. Each of the heavy and light chain variable regions is a member of a library (or a plurality) of variable regions (see col. 62-63).

Applicant argues "the first and second pluralities of variable polynucleotides each encode a plurality of polypeptides (i.e., the first plurality of variable polynucleotides encodes a first plurality of polypeptides and the second plurality of variable polynucleotides encodes a second plurality of polypeptides). Both the first and second pluralities are variable, and thus neither the nucleotide sequences nor the polypeptide sequences encoded by them are "fixed"" on pg 2 and 3 of the reply filed on 3/31/06.

Applicant argues that the '108 patent's teaching of the "fourth approach" of generating libraries of antibodies (col. 7, line 5+) does not anticipate the claimed invention, because the "fourth approach" teaches that one of the heavy and light chains "is kept fixed" (col. 7, line 9+). This is not found persuasive, because in the "fourth approach" taught by the '108 patent, either the heavy or the light variable regions (reads on the first and second variable polypeptides) are derived from a library of heavy variable regions or a library of light variable regions (see Examples 22 and 46). For example, Example 22 uses antibody heavy chain variable regions and light chain variable regions derived from repertoires (i.e. libraries or pluralities) of heavy and light chain variable regions. Thus, each of the heavy chain and light chain variable is a member of a first (or second) plurality of variable polypeptides.

Applicant also seems to argue that the claimed library of vectors comprises different vectors comprising different first variable polynucleotides (a plurality) and different second variable polynucleotides (a plurality), i.e. the library of vectors comprises two pluralities of variable polynucleotides.

The reference ('108 patent) does specifically teach a library of vectors comprising both various heavy chain variable regions (a first plurality) and various light chain variable regions (a second plurality). For example, the reference teaches a vector comprising at least two cloning sites comprising restriction sites, ribosome binding site (RBS), and the antibody variable regions (reading a the first and second plurality) (see Figure 45). Although Figure 45 depicts a vector with one particular heavy and one particular light chain variable region, such a vector can be used to generate a library of vectors that comprises different heavy and light chain variable regions. Indeed, the reference teaches the generation of such a library of vectors in detail (see Examples 26 and 39). For example, Example 39 teaches the following (see col. 88, lines 44+):

> "This example shows that functional Fv fragments can be expressed on the surface of bacteriophage by non-covalent association of VH and VL domains. The VH domain is expressed as a gene III fusion and the VL domain as a soluble polypeptide. Thus Fv fragments can be used for all the strategies discussed for Fab fragments including dual combinatorial libraries (example 26)."

In other words, the reference teaches the vector depicted in Figure 45 (corresponding to Example 39) can be used to express both the variable heavy chain domains (the first plurality) and variable light chain domains (the second plurality) to form library of antibody fragments via non-covalent association. Specifically, the reference teaches the vector depicted in Figure 45 can be used to generate dual combinatorial libraries (see col. 88, lines 48+), i.e. a vector library comprising two pluralities of variable regions.

Example 26 (as alluded to in Example 39) of the reference provides additional teachings of generating a library of vectors that encode different heavy and light chain variable regions. Specifically, Example 26 recites the heavy and light chains of antibody fragments can be encoded together in the same vector or in different vectors (see col. 68, lines 22+). Furthermore, Example 26 teaches the generation of antibody libraries with different heavy and light chain variable regions with both the heavy and light chains encoded by the same vector (see bridging para. of Cols. 68 and 69). In addition, Example 26 teaches that the libraries of heavy and light chains (reads on the first and second pluralities) can be expressed from the same vector using different promoters as separate transcripts (see col. 69, lines 7+), hence separate translations that require separate ribosome binding sites on the same vector.

As demonstrated above, the reference ('108 patent) teaches every elements of the present invention, and therefore, anticipates the present invention of a library of vectors comprising two cloning sites, which comprises two repertoires of different variable polynucleotides.

6. Claims 1-3, 11-12, 15-16 are rejected under 35 U.S.C. **102(a)** as being anticipated by EP 844306 A1 (hereinafter referred to as the **'306 patent**). The previous rejection is maintained for the reasons of record advanced on page 3 of the office action mailed on 12/29/2005.

Discussion and Answer to Argument ('306 patent)

7. *Applicant argues that the examiner failed to consider all of the limitations of the instant claims and thus mis-characterized the instant claims (Pg 2-3 of the reply filed 3/31/06), as recited supra.*

8. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record):

As applicant has noted in the reply filed on 3/31/06 that the'108 patent and the '306 patent claim priority from the same U.K. patent application and that the disclosures are highly similar (see pg 3 of the reply). Applicant states that the '108 patent fails to anticipate the instant claims for the same reasons that '306 patent fails to anticipate the instant claims. Therefore, applicant's traversal over the '306 patent is addressed by the above discussion of the '108 patent.

9. Claims 1-3, 11-16 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,172,197 B1 (McCafferty et al) (hereinafter referred to as the **'197 patent)**. The previous rejection is maintained for the reasons of record advanced on page 6 of the office action mailed on 12/29/2005.

Discussion and Answer to Argument ('197 patent)

10. *Applicant argues that the examiner failed to consider all of the limitations of the instant claims and thus mis-characterized the instant claims (Pg 2-3 of the reply filed 3/31/06), as recited supra.*

11. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record):

As applicant has noted in the reply filed on 3/31/06 that the '197 patent, the'108 patent and the '306 patent claim priority from the same U.K. patent application and that the disclosures are highly similar (see pg 3 of the reply). Applicant states that the '197 patent fails to anticipate

the instant claims for the same reasons that '306 patent and the '108 patent fail to anticipate the instant claims. Therefore, applicant's traversal over the '197 patent is addressed by the above discussion of the '108 patent.

Claim Rejections Maintained

Claim Rejections - 35 USC § 103

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. Claims 1-3, 11-12, 15-16 are rejected under 35 U.S.C. 103(a) as being obvious over either US Patent 5,969,108 or US Patent 6,172,197. The previous rejection is maintained for the reasons of record advanced on page 8 of the office action mailed on 12/29/2005.

Discussion and Answer to Argument

14. Applicant argues the '108 patent and '197 patent fail to suggest the instant claims. Applicant further argues nothing in either the '108 patent or the ' 197 patent teaches or suggests libraries with a pool of H chains combined with a pool of L chains (as recited in the instant claims). There is no evidence on the record of any such motivation to modify the teachings of the cited references to arrive at the claimed libraries (Pg 4-5 of the reply filed 3/31/06).

15. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record):

First, applicant's statement of "libraries with a pool of H chains combined with a pool of L chains (as recited in the instant claim)" (pg 5 of the reply) is not a recited limitation in the instant claims. In response to applicant's argument that the references fail to show certain

features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "a pool of H chains combined with a pool of L chains") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Second, contrary to applicant's assertion that "*There is no evidence on the record of any such motivation to modify the teachings of the cited references to arrive at the claimed libraries (Pg 4-5 of the reply filed 3/31/06*", the previous office action did provide evidence for motivation. In the previous office (bridging para. of pg 9-10), the examiner states "A person of skilled in the art would have been motivated to use the variable first member of polynucleotides and variable second polynucleotides into the same vector, because such vectors will have more diversity and express polyclonal antibodies" (emphasis added). As discussed by the previous office action, the '108 patent teaches the advantages of generating antibody fragment libraries via non-covalent association of the heavy and light chain variable regions, so that different combinatorial strategies can be used to generate diverse antibody fragments (col. 69, lines 1+; col. 68, lines 10+). By inserting the heavy and light chain variable regions in different cloning sites on the same vector with different transcription/translation initiation sites, the two variable regions (heavy and light) can be expressed separately, and then paired together to generate high antibody diversity (see top of Col. 69).

Not only does the '108 patent provide motivation to generate libraries of vectors comprising two pluralities of variable regions, but the patent also teaches such libraries of antibodies fragments (encoded by libraries of vectors) comprising both heavy and light chain

variable regions using dual combinatorial libraries (see col. 88, lines 48+), i.e. pools or pluralities of both heavy chain and light chain variable regions. The reference also teaches various vectors that can be used for generating the dual combinatorial libraries. For example, the '108 patent teaches both of the heavy and light chains are 5'-flanked by rbs and single sequence (see above discussion and Figure 45 of the '108 patent), which is contrary to applicant's assertion that the '108 patent teachs "the H and L chains are not both 5'-flanked by an rbs and single sequence" (pg 4 of applicant's replay).

Therefore, not only does the reference anticipates the instant claimed invention, but the reference also provides strong motivation to generate antibody fragment libraries using vectors that encode both different heavy and light chain variable regions. As discussed above, the '108 patent provides ample motivation to generate vectors comprising variable regions of both heavy and light chains with each of the heavy and light chain fragment derived from separate libraries.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

PETER PARAS, JR.
PRIMARY EXAMINER